Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement 510(k)s; Final Guidance for Industry

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This document supersedes "Guidance Document for Testing Orthopedic Bone Cement" dated 11/1/93.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Orthopedic Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Mr. Hany W. Demian at (301) 594-2036, ext.184 or by electronic mail at hwd@cdrh.fda.gov.

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Purpose / Background

On October 14, 1999, FDA issued an order reclassifying the polymethylmethacrylate (PMMA) bone cement from class III (premarket approval) into class II (special controls). This document is the special controls guidance for the PMMA bone cement. This document also serves to update the information presented in *"Guidance Document for Testing Orthopedic Bone Cement"* dated November 1, 1993.

FDA has determined that special controls, when combined with the general controls and the specific information in the *510(k) Content* section, are sufficient to provide reasonable assurance of the safety and effectiveness of the PMMA bone cement. Thus, a manufacturer who intends to market a device of this generic type must (1) conform with the general controls of the Food, Drug & Cosmetic Act, including the premarket notification (510(k)) requirements described in 21 CFR 807.81, (2) address the specific risks to health associated with the PMMA bone cement, and (3) receive a substantial equivalence determination from FDA prior to marketing the device.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Scope

FDA identifies the generic PMMA bone cement (luting agent) as an orthopedic device classified under 21 CFR 888.3027, product code LOD. It is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone. This generic type of device is made from polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene

Risks to Health

FDA has identified the following 8 risks to health associated with the use of PMMA bone cement:

1. bone cement implantation syndrome
2. handling problems
3. loosening or migration of the device
4. infection and fever
5. user reaction
6. adverse tissue reaction
7. pain and/or loss of function
8. revision

Controls

FDA believes that the controls below, when combined with general controls and the specific information in the *510(k) Content* section below, will address the above identified risks to health associated with the use of the device. Manufacturers should demonstrate that their device complies with either the specific recommendations of this guidance or with an alternate means to address the above identified risks to health and to provide reasonable assurance of the safety and effectiveness of the device.

Manufacturers who reference recognized standards as part of their 510(k) submission should provide statements regarding conformance or "Declarations of Conformity" under the FDA Modernization Act of 1997. Because statements afford greater flexibility for device developers than "Declarations of Conformity," submitters of 510(k)s should consider using guidance documents and consensus standards in this manner. For information regarding declarations of conformity, refer to FDA's "Guidance on Recognition and Use of Consensus Standards," which is available on our website at http://www.fda.gov/cdrh/ost/guidance/321.html.

1. FDA guidance documents:

a. "Draft Guidance Document for the Preparation of Premarket Notification (510(k)) Applications for Orthopedic Devices - The Basic Elements"
b. "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part I: Evaluation and Testing"
c. "510(k) Sterility Review Guidance of 2/12/90 (K90-1)"

2. American Society for Testing and Materials (ASTM) and International Organization for Standardization (ISO) Consensus Standards:

a. ASTM F 451-99, "Standard Specifications for Acrylic Bone Cement"
b. ASTM D 638-00, "Standard Test Method for Tensile Properties of Plastics"
c. ASTM D 732-99, "Standard Test Method for Shear Strength of Plastics by Punch Tool"
d. ASTM D 790-00, "Standard Test Method for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials"
e. ASTM D 2990-95, "Standard Tensile, Compressive, and Flexural Creep and Creep Rupture of Plastics"
f. ASTM E 399-97, "Standard Test Method for Plane-Strain Fracture Toughness of Metallic Materials"
g. ASTM E 647-00, "Standard Test Method for Measurement of Fatigue Crack Growth Rates"
h. ISO 5833:1992, "Implants for surgery - Acrylic resin cements"

510(k) Content

The 510(k) content information below is specific to PMMA bone cement. Therefore, the guidance serves as a supplement to other FDA publications on premarket notification (510(k)) applications and should not be construed as a replacement for these documents. For general 510(k) information, you should refer to 21 CFR 807 or access the multiple 510(k) guidances through our website at http://www.fda.gov/cdrh/guidance.html.

The following specific information should be provided for a PMMA bone cement 510(k):

I. INTENDED USE/INDICATIONS FOR USE

Provide the intended use/indications for use. Bone cements, for which appropriate information has been submitted, may be cleared for use in arthoplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prostheses to living bone for patients with rheumatoid arthritis, osteoarthritis, traumatic arthritis, osteoporosis, avascular necrosis, collagen disease, severe joint destruction secondary to trauma or other conditions, and revision surgeries.

II. DEVICE DESCRIPTION

Provide a complete description of the final sterilized PMMA bone cement, including the chemical and physical properties of the liquid and powder components and the cured bone cement. PMMA bone cement is a self-curing, two component system consisting of a liquid and powder components. Typically, the liquid component contains the monomer, accelerator, and the inhibitor. The powder contains the polymer, radio-opacifier and the initiator. A table comparing the similarities and differences in these parameters between the proposed product and a legally marketed device should be presented. Component ratios should be compared for the proposed product and commercially available bone cement. The final product release specifications for

each chemical should be provided along with other specifications for the dough, working, set time, and residual monomer limit and elution of monomer limits for cured bone cement.

III. DEVICE CHARACTERIZATION

Device characterization should be provided on the final sterilized PMMA bone cement.

A. Biocompatibility – Biocompatibility data should be addressed for any bone cement composition. A standard battery of toxicological tests is recommended in the ISO-10993, "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing." This guidance suggests short term and long term biological tests that might be applied to evaluate the safety of any bone cement.

For additional information, please refer to the guidance, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices – 5/1/95 – (G95-1) " which can be obtained at http://www.fda.gov/cdrh/g951.html.

B. Physical and Chemical Characterization

Physical and chemical analyses are used to characterize the liquid, powder, and cured bone cement. Appendix 1 lists important information including assembly and application of the cement in which the dough, working, and set times are characterized (ASTM 451- and ISO 5833). Next, main ingredients, additives, and trace elements found in a bone cement composition should be identified along with their respective amounts. During initial mixing and after polymerization, residual monomer levels and elution of monomer should be evaluated by gas chromatography or any other applicable method (testing performed at 1 hour, 24 hours, and 72 hours after polymerization). Molecular weight of the powder and cured cement should be established by gel permeation chromatography or solution viscosity measurements. If the polymerization process is other than the free radical polymerization, then the degree of polymerization should be evaluated. Other physical properties that should be characterized include the powder's morphology, size distribution, and dispersion of the polymer and additives. This is typically achieved by light microscopy or Scanning Electron Microscopy (SEM).

C. Mechanical Testing

Several in-vitro mechanical test methods are used to evaluate the material's integrity. Appendix 2 includes mechanical characterization (i.e., modulus, fatigue, fracture toughness, fatigue crack propagation (optional), flexular strength, compressive strength, shear strength, tensile strength, and creep). Testing of a concurrent control (e.g., similar commercially available bone cements) is highly recommended because the investigator and method of preparing the specimens can greatly influence the test results that are reported. See Section VI for complete test report suggestions.

After mechanical testing, the morphology of the fracture surface should be considered. These analyses include: 1) porosity measurements of the fracture surface and the bulk material; 2) additive dispersion measurements on the fractured surface; and 3) failure analysis of the fracture surfaces.

D. Shelf-life, Product Expiration Dating and Storage Conditions

A bone cement's shelf-life should be established by either real time storage or by a validated accelerated testing protocol (Appendix 2). The appropriateness of accelerated stability data is determined by the device composition and validation to real time aging. The value of accelerated stability test data relies on identical decomposition mechanisms at both standard and elevated temperatures. Data supporting the expiration date for a product should be submitted along with how the product should be stored before use. Such data should be collected from at least three production lots. Stability studies should monitor the critical parameters (physical and mechanical properties) of a device that are required to insure it will perform consistently during its entire shelf-life.

IV. NEED FOR CLINICAL DATA

There may be several situations under which clinical data are considered necessary to evaluate safety and effectiveness, such as a new intended use, a specific change to a bone cement's chemical formulation, or the addition of any new chemicals to a bone cement's formulation. The purpose of the flowchart in Appendix 3 is to provide guidance for when clinical data may be needed to support a change to an existing bone cement formulation. There are several bone cements currently available in the U.S. that have similar formulations; however, there are differences between them which include the types and morphologies of polymers, types and amounts of radio-opacifiers, and amounts of initiators, accelerators, and inhibitors. The flowchart provides several different scenarios where clinical data may or may not be needed.

A few examples are presented below to demonstrate the use of the flowchart.

- A change is made to an existing formulation where a new chemical is added. Information related to any published clinical data supporting the use of this new chemical or previously cleared bone cement containing the specific new chemical component should be provided. If no published clinical data exist, then prospective clinical data may be needed to support clearance.

- A change is made to an existing bone cement formulation where the change is to the ratio(s) of the known chemicals used in the bone cement formulation. Information related to any clinical experience with this new formulation should be provided. If no published clinical data exist, then prospective clinical data may be needed to support clearance.

- A change is made to the morphology of the powder, for example, milling of the powder to affect the handling characteristics. If no published clinical experience with this product or a similar product exits, then prospective clinical data may be needed to support

clearance.

Because these devices meet the definition of significant risk under 21 CFR 812.3(m), clinical studies should be performed under the investigational device exemptions (IDE) regulations defined under 21 CFR 812.20. An IDE application is required to be submitted to, and approved by, FDA prior to initiating a clinical study.

V. LABELING

All labeling information for a PMMA bone cement should be supplied, including individual package labeling, package inserts, and available promotional literature. The outside box label should clearly identify the storage conditions for the bone cement and if equilibration (i.e., time for the components to reach optimal temperature for use) of the bone cement is needed before use. The package insert and surgical technique should specify the intended use of the device, contraindications, warnings, precautions, and directions for use.

In addition to the general labeling requirements for a 510(k), the following statements should be included for any bone cement:

A. Contraindication Section

PMMA Bone Cement is contraindicated in the presence of active or incompletely treated infection, at the site where the cement is to be applied.

B. Warnings Section

1. Adverse patient reactions affecting the cardiovascular system have been associated with the use of bone cements. Hypotensive reactions have occurred between 10 and 165 seconds following application of bone cement; they have lasted from 30 seconds to 5 or more minutes. Some have progressed to cardiac arrest. Patients should be monitored carefully for any change in blood pressure during and immediately following the application of bone cement.

2. The liquid monomer is highly volatile and flammable. The operating room should be adequately ventilated to eliminate as much monomer vapor as possible. Ignition of monomer fumes caused by use of electrocautery devices in surgical sites near freshly implanted bone cements has been reported.

3. Caution should be exercised during the mixing of the two components to prevent excessive exposure to the concentrated vapors of the monomer, which may produce irritation of the respiratory tract, eyes, and possibly the liver. Personnel wearing contact lenses should not be near or involved in mixing this bone cement.

C. Precautions Section

1. The product should not be used after the expiration date printed on the package.

2. The liquid component has caused contact dermatitis in its handling and mixing. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of this complication.

3. The liquid component is a powerful lipid solvent. This liquid component should not be allowed to come into contact with rubber or latex gloves. Wearing of a second pair of gloves and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The mixed bone cement should not make contact with the gloved hand until the cement has acquired the consistency of dough. This usually occurs between one and two minutes after the liquid and powder components have been mixed.

4. Inadequate fixation or unanticipated postoperative events may affect the cement-bone interface and lead to micromotion of cement against bone surface. A fibrous tissue layer may develop between the cement and the bone, and loosening of the prosthesis may occur. Long-term follow-up is advised for all patients on a regularly scheduled basis.

5. Polymerization of the bone cement is an exothermic reaction, which occurs while the cement is hardening *in situ.* The released heat may damage bone or other tissues surrounding the implant.

6. Extrusion of the bone cement beyond the region of its intended application may occur.

7. The safety of the bone cement in pregnant women or in children has not been established.

8. The polymer component may be disposed of in an authorized waste facility. The liquid component can be evaporated under a well-ventilated hood or absorbed by an inert material and transferred in a suitable container for disposal.

D. Adverse Event Section

1. Serious adverse events, some with fatal outcome, associated with the use of acrylic bone cements include myocardial infarction, cardiac arrest, cerebrovascular accident, and pulmonary embolism.

2. The most frequent adverse reactions reported with acrylic bone cements are transitory fall in blood pressure, thrombophlebitis, hemorrhage and hematoma,

loosening or displacement of the prosthesis, superficial or deep wound infection, trochanteric bursitis, and short-term cardiac conduction irregularities. Other adverse reactions include heterotopic new bone formation and trochanteric separation.

3. Other potential adverse events reported for acrylic bone cements include: pyrexia due to an allergy to the bone cement, hematuria, dysuria, bladder fistula, delayed sciatic nerve entrapment due to extrusion of the bone cement beyond the region of its intended application, and adhesions and stricture of the ileum due to the heat released during polymerization.

E. Instructions and Training Section

1. The instructions for use should include a handling time versus temperature chart to give the user information regarding how fast the bone cement will polymerize at a given temperature and humidity.

2. The surgeon should, by specific training and experience, be thoroughly familiar with the properties, handling characteristics, and application of bone cements. Because the handling and curing characteristics of this cement vary with temperature, humidity, and mixing technique, they are best determined by the surgeon's actual experience.

3. The sponsor should provide adequate instructions and training procedures regarding the use of their bone cement for which the clearance is being sought.

VI. COMPLETE TEST REPORT SUGGESTIONS

Aside from the general information that should be included in any complete test report, there are some specific items for consideration as part of the test report.

A. Because these variables may affect the reported in-vitro mechanical properties, the test report should include the following information regarding the preparation of the test specimens:

1. mixing – mixing date and temperature of the environment and mixing surfaces throughout the procedure
2. centrifugation - amounts of ingredients, monomer temperature, rate (revolutions per minute), and time
3. hand mixing, mechanical (machine) mixing, or vacuum mixing - amounts of ingredients, order of assembly, pressure, rate (beats per minute), duration, and geometry of mixer (rotar, container)
4. mold – design, material, and temperature
5. machined - number of specimens broken during machining
6. finishing effects - number of specimens rejected due to surface defects

7. aging (curing) - sequence stages chronology of events, duration, environment, and temperature

B. The test report should include all mechanically tested specimens.

C. The test report should include a discussion of all specimens prepared but not tested, including the number of rejected specimens, the reasons for rejection, the evaluation methods, and the rejection pass/fail criteria.

APPENDIX 1

Physical and Chemical Methods of Analyses.

	Suggested Analyses	Examples of Test Methods
Assembly and Application	Mix Liquid & Powder Components	ASTM F451-95, ISO 5833-92
	Dough Time	ASTM F451-95, ISO 5833-92
	Setting Time	ASTM F451-95, ISO 5833-92
	Viscosity: Pre-Dough Stage Extrusion Dough Stage Intrusion	ASTM F451-95, ISO 5833-92 ASTM F451-95, ISO 5833-92
Chemical Composition	Ingredients: chemical formula, structure, additives, etc.	Liquid-NMR, FTIR, HPLC/MS
	Type of radio-opacifier	TGA/gross pyrolysis
	Purity or trace elements	ICP/MS, GC/FTIR/MS, titration
	Residual low MW molecules	GC, HPLC/GPC, liquid-NMR
	Leachables (e.g., low MW molecules)	GC, HPLC/GPC
Molecular Weight and Polymer Structure	MW by viscous flow	Viscosity measurements (e.g., solution)
	MW: Polydispersity, M_n, M_w	GPC with refractive index detector using polystyrene as standard material
	Branched, linear, or crosslinked	Solubility, swelling, liquid-NMR
	% Crystallinity (if applicable)	X-ray diffraction, DSC
	Crystallization temperature (if applicable)	DSC, DMA
	Glass transition temperature (Tg) (if applicable)	DSC, DMA
Physical Properties	Powder's morphology, size characterization and dispersion of polymer and additives	Light microscopy, SEM of powder and cured cement
	Porosity characterization	Scanning Acoustical Microscopy of bulk cement (e.g., SLAM, C-SAM) and serial sectioning of the cured cement
	Dimensional changes during curing (shrinkage)	Volume measurement
	% Water absorption (swelling)	Saturation testing
	Aging due to fluid absorption and polymerization	Mechanical testing (Appendix 2)
Stability of Components	Change in monomer viscosity due to artificial aging	ASTM 451 - 95
	Change in benzoyl peroxide levels	Titration method, FTIR, GC
Thermal Properties	Maximum polymerization temperature	ASTM F451 - 95, ISO 5833 - 92

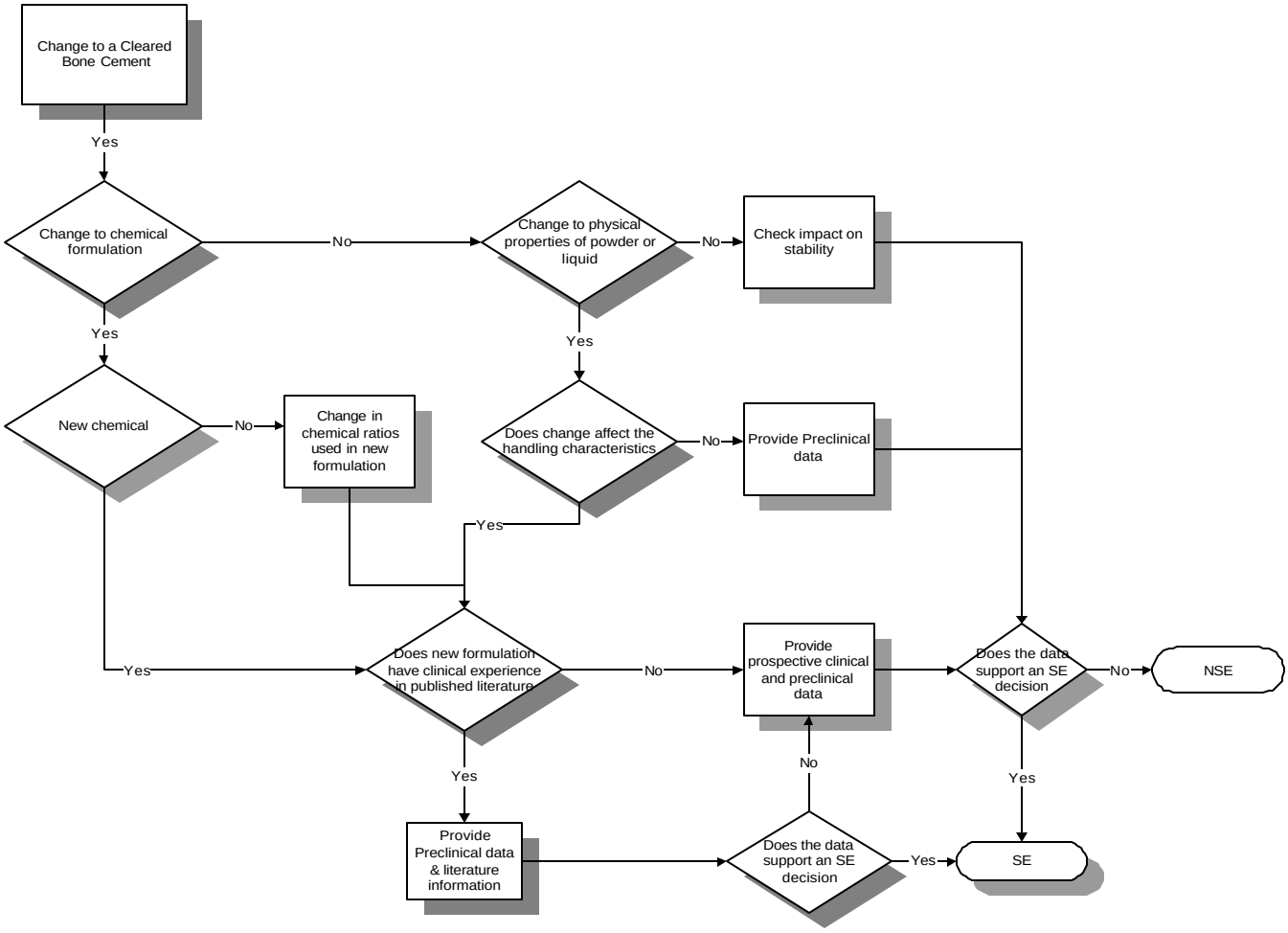
C-SAM=C-mode scanning acoustical microscopy
DMA=Dynamic mechanical analysis
DSC=Differential scanning calorimetry
FTIR=Fourier transform infrared
GC=Gas chromatography
GPC=Gel permeation chromatography
HPLC=High-performance liquid chromatography
ICP=Inductively coupled plasma
MS=Mass spectroscopy
MW=Molecular weight
NMR=Nuclear magnetic resonance
SEM=Scanning electron microscopy
SLAM=Scanning laser acoustical microscopy
TGA=Thermogravimetric analysis

APPENDIX 2
Mechanical Properties and Shelf Life

Mechanical Properties		Suggested Types of Tests	Examples of Test Methods
Modulus	Flexural	4-point bending	ISO 5833-92
	Compressive	Uniaxial compression	ISO 5833-92 , ASTM F451-95
	Tension	Uniaxial tension	ASTM D638-91 - rectangular or cylindrical specimen
Cyclic Fatigue Properties		Uniaxial Tension/Compression or Tension/Tension	ASTM D638–91 - rectangular or cylindrical specimen - frequency – physiologically relevant or justified level - sinusoidal wave form - load control - stress levels which are similar to expected in vivo stresses
		3 or 4-point Bending	Use rectangular specimens
Fracture Toughness, K_{IC}		Compact Tension	ASTM E399–90
		Notched Bending	Compact tension or single-edge notched
Fatigue Crack Propagation (optional)		Compact Tension	ASTM E647- 95
Static Strength	Flexural	4-point bending	ISO 5833-92
	Compressive	Uniaxial compression	ISO 5833-92, ASTM F451-95
	Tensile	Uniaxial tension	ASTM D638–91 – rectangular/cylindrical specimens
	Shear	Single Shear (cement-cement)	ASTM D732-93
Viscoelasticity		Uniaxial Compressive Creep	ASTM D2990-95 or compressive creep of cylindrical specimens
		Dynamic Mechanical Analysis (optional mechanical testing should be considered if further evaluation is needed)	DMA
Shelf Life		Measurement of mechanical properties of hardened cement after components have been aged over time	Real-Time storage or a validated accelerated aging condition of sterilized liquid and powder components. Perform testing on cured bone cement.

APPENDIX 3

Bone Cement Decision FlowChart*



*This flowchart only applies when the device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer and metallic prosthetic implants to living bone.

Definitions

- chemical formulation - chemicals used in specified ratios to make up a bone cement formulation
- new chemical - a chemical previously not approved in a bone cement formulation
- chemical ratios - chemical amounts used in formulation
- physical properties - morphology, size, and dispersion of polymer and additives in cement
- SE - substantial equivalence
- NSE- not substantially equivalent